

REMARKS/ARGUMENTS

In response to the Office Action of August 2, 2006, Applicant has amended the claims, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

By this amendment, claims 12 and 15 have been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims and the claims as presented prior to this amendment, in one or more continuation applications.

Claims 4, 5, 8 and 12-15 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly not supported by the written description. In order to advance prosecution of this application Applicant has amended claim 4 to recite:

"A method for the treatment of rheumatoid arthritis in a patient in need of such treatment comprising administering to the patient an effective amount of a CD25 binding molecule; wherein the CD25 binding molecule comprises:

(a) first domain the hypervariable regions CDR1, CDR2 and CDR3; the CDR1 having the amino acid sequence Arg-Tyr-Trp-Met-His (SEQ ID NO:1), the CDR2 having the amino acid sequence Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly (SEQ ID NO:2) and the CDR3 having the amino acid sequence Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe (SEQ ID NO:3) and

(b) a second domain comprising in sequence the hypervariable regions CDR1', CDR2' and CDR3', the CDR1' having the amino acid sequence Ser-Ala-Ser-Ser-Ile-Ser-Tyr-Met-Gln (SEQ ID NO:4), the CDR2' having the amino acid sequence Asp-Thr-Ser-Lys-Leu-Ala-Ser (SEQ ID NO:5) and the CDR3' having the amino acid sequence His-Gln-Arg-Ser-Ser-Tyr-Thr (SEQ ID NO:6)."

Support for claim 4 as amended may be found throughout the specification, e.g., page 1, final paragraph, to page 2, first paragraph. Applicant respectfully submits that claim 4 as presently amended, as well as claims 8, 13, and 14 which depend therefrom, are fully supported by the written description of this application. Withdrawal of the

rejection under the written description requirement of 35 U.S.C. 112, first paragraph, is therefore warranted.

Claims 4, 5, 8, and 12-15 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over WO/89/09622 in view of Kovarik et al. (1997) *Transplantation* 64(12):1701-1705. WO 89/09622 has been cited for teaching a method of treating rheumatoid arthritis (RA) comprising administering an effective amount of a CD25 binding molecule. The reference had also been cited for teaching the coadministration of a further substance effective in the treatment of RA, e.g., methotrexate.

Kovarik et al. has been cited for teaching a CD25 binding molecule comprising a CDR1, CDR2, and CDR3 having the amino acid sequences Arg-Tyr-Trp-Met-His, Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe, respectively. Kovarik et al. has also been cited for teaching that serum concentrations of basiliximab sufficient to saturate IL-2 receptors were achievable.

Since the '622 reference teaches the use of a chimeric anti-IL2 receptor antibody for the treatment of RA, while Kovarik et al. teaches the chimeric anti-IL2 receptor antibody basiliximab which comprises the CDRs of the instant claims, the Examiner has concluded that the combined teachings of the two references amount to substitution of obvious equivalents. The Examiner has further posited that because the Kovarik et al. reference teaches that basiliximab can achieve IL2 receptor saturation and the antibody is well tolerated, basiliximab could be considered not only an equivalent of the antibody of the '622 patent but a preferred substitution of such antibody.

Applicants traverse the rejection of claims 4, 5, 8 and 12-15 under 35 U.S.C. §103(a) for the following reasons. The role of IL-2 in the immunopathogenesis of rheumatoid arthritis (RA) has been greatly debated. As of the priority date of the present application, numerous conflicting theories and data had been published. For example, serum Interleukin-2 (sIL-2) and serum Interleukin-2 receptor (sIL-2R) levels were found to correlate with RA disease activity in some studies, but not others. See Wood, et al. (1988) "Serum interleukin-2 receptor in rheumatoid arthritis: a prognostic indicator of disease activity?" *J. Autoimmun.* 1:353-61, an abstract of which is provided

herewith as Exhibit A; Keystone, et al. (1988) "Elevated soluble interleukin-2 receptor levels in the sera and synovial of with patients with rheumatoid arthritis. *Arthritis Rheum.* 31(7): 844-9, an abstract of which is provided herewith as Exhibit B; Crilly A. et al. (1993) "Serum concentrations of soluble interleukin-2 receptor in patients with rheumatoid arthritis: effect of second line drugs. " *Ann. Rheum. Dis.* 52:58-60, an abstract of which is provided herewith as Exhibit C; and Ward M.M., et al. (1994) "Serial measurements of serum interleukin-2 receptor levels in patients with rheumatoid arthritis: Limited evidence for a role of T cell activation in clinical exacerbations" *Clin. Immunol. Immunopathol.* 73(3):296-304, an abstract of which is provided herewith as Exhibit D.

Other studies showed that IL2 levels, IL-2 mRNA levels, and IL-2 receptor (IL-2R) mRNA levels were low or not detected in synovial fluids and synovial tissues from patients with RA. See Chen, E. et al. (1993) "Restricted cytokine expression in rheumatoid arthritis" *Arthritis Rheum.* 36:901-10, an abstract of which is provided herewith as Exhibit E, and Firestein G.S., et al. (1998) "Cytokines in chronic inflammatory arthritis. I. Failure to detect T cell lymphokines (interleukin 2 and interleukin 3) and presence of macrophage colony-stimulating factor (CSF-1) and a novel mast cell growth factor in rheumatoid synovitis" *J. Exp. Med.* 168:1573-86, an abstract of which is provided herewith as Exhibit G.

Still other studies demonstrated that Tac (CD25) was virtually absent in all areas and tissues in synovial membranes of RA patients. See El-Gabalawy, H.S. (1992) "Immunohistologic study of T-cell receptor delta-chain expression in rheumatoid synovial membranes" *Sem. Arthritis Rheum.* 21:239-45, an abstract of which is provided herewith as Exhibit F.

The undersigned will forward full copies of the references forthwith, in a supplementary response.

It is respectfully submitted that although the cited '622 publication teaches a method of treating rheumatoid arthritis by administering a CD25 binding molecule, no *in vivo* data is provided to support such assertion. The '622 document only provides *in vitro* data with respect to showing activity of the anti-Tac antibody on the IL-2 receptor. See WO 89/09622, pages 26-28.

Moreover, Applicant respectfully submits that the Kovarik et al. reference only goes so far as to teach that administration of basiliximab is well tolerated, nonimmunogenic and provides immunoprophylaxis to patients in the first month following renal allografts. The reference makes no mention of the use of basiliximab in any other condition or disease state.

Applicant respectfully submits therefore, that one skilled in the art at the time the invention was made, having WO 89/09622 and Kovarik (1997) in hand, as well as the evidence provided herewith as Exhibits A-G, would not have found the presently claimed invention obvious.

Summarizing, at the time the invention was made, a number of published reports taught that sIL-2 and sIL-2R levels did not correlate with RA disease activity; that levels of IL2 could not be detected in RA joints; that IL-2 levels and both IL2 and IL2-R mRNA levels were low or not detected in synovial fluids and synovial tissues from patients with RA; and that Tac (CD25) was virtually absent in all areas and tissues in synovial membranes of RA patients. Therefore, the teaching of the '622 document, where a method of treating RA with an anti-Tac antibody is merely asserted and supported by only a single *in vitro* binding experiment, combined with the limited teaching in Kovarik et al (1977) of treating renal transplant patients with basiliximab, would not have suggested or motivated one skilled in the art to make and use the present invention.

There is simply no teaching in any of the references of record in this application that serum concentrations of basiliximab necessary to saturate the IL-2 receptor to suppress transplant rejections as taught by Kovarik et al. 1997, correlate to effectiveness in treating RA. Indeed, administering basiliximab in order to treat RA would have seemed counterintuitive to one skilled in the art when considering the published teachings that there was limited evidence for a role of T cell activation in patients with RA, and that only a low percentage of the intra-articular T cells express Tac antigen in the first instance.

Once a *prima facie* case of obviousness has been established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie*

case. *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897,1901 (Fed. Cir. 1990)(*in banc*). Rebuttal evidence may take many different forms, including evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. *In re Oelrich*, 579 F.2d 86, 91-92, USPQ210, 214 (CCPA 1978). Once an applicant has presented rebuttal evidence, the examiner should reconsider any initial obviousness determination in view of the entire record, which reconsideration should not be influenced by any earlier conclusion. See *In re Piasecki*, 745 F.2d 1468, 1472-73, 223USPQ 785, 788 (Fed. Cir. 1984); *In re Eli Lilly & Co.* 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

Applicant has presently come forward with rebuttal evidence showing the state of the art, and the beliefs of those of skill in the art, at the time the invention was made. In light of the conflicting theories and evidence concerning the role of IL-2 in the immunopathogenesis of RA, available at the time the invention was made (see Exhibits A-G), along with the remarks hereinabove, it is respectfully submitted that one skilled in the art would not have been motivated to treat RA using an anti CD25 antibody as presently claimed with any reasonable expectation of success.

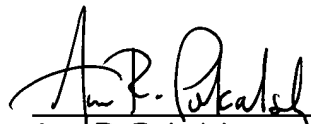
At most, the combination of teachings provided by the '622 reference and Kovarik et al., when viewed with the state of the art and the beliefs of those skilled in the art at the time the invention was made, could only amount to an invitation to experiment, i.e., an "obvious to try" situation. "Obvious to try" however, is not the standard under 35 U.S.C. 103. *In re Fine*, 837 F.2d 1071, 5 UAPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of the rejection of claims 4, 5, 8 and 12-15 under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks, amendments, and exhibits, it is firmly believed

that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Novartis
Corporate Intellectual Property
400 Technology Square
Cambridge, MA 02139
(617) -871-3105


Ann R. Pokalsky
Attorney for Applicants
Reg. No. 34,697

Date: February 2, 2007



A service of the National Library of Medicine
and the National Institutes of Health

www.pubmed.gov

My NCBI
[\[Sign In\]](#) [\[Regis\]](#)

All Databases

PubMed

Nucleotide

Protein

Genome

Structure

OMIM

PMC

Journals

Book

Search for

Limits

Preview/Index

History

Clipboard

Details

Display Show Sort by Send to

All: 1 Review: 0 ☒

☐ 1: J Autoimmun. 1988 Aug;1(4):353-61.

[Links](#)

Serum interleukin-2-receptor in rheumatoid arthritis: a prognostic indicator of disease activity?

Wood NC, Symons JA, Duff GW.

University Department of Medicine, R.D.U., Northern General Hospital, Edinburgh.

Interleukin-2 (IL-2) is an important growth factor for T lymphocytes. Its effects are mediated by cell surface receptors (IL-2 R) expressed on activated T cells. Receptor protein can be shed from cell membranes and the soluble form (sIL-2 R) is detectable by enzyme linked immunosorbent assay (ELISA). We have studied serial levels of sIL-2 R in the sera of patients with rheumatoid arthritis (RA). In 13 patients with active disease, the mean serum level of sIL-2 R was raised compared to age-matched healthy controls. In 48 samples taken at different times from 13 patients, serum sIL-2 R correlated significantly with Ritchie joint index, duration of early morning stiffness, patient pain score, physician's assessment, erythrocyte sedimentation rate (ESR) and platelet count. In individual patients, serial sIL-2 R serum levels fell with treatment preceding clinical improvement. In four patients where serum sIL-2 R levels fell and clinical improvement occurred, subsequent spontaneous increases of serum sIL-2 R level preceded increased clinical disease activity by up to 2 weeks. Serum sIL-2 R level in RA probably reflects activation of underlying immunopathogenic mechanisms and appears to be an excellent monitor of clinical disease activity. More importantly, a rising level may also predict exacerbation of disease activity.

PMID: 3266993 [PubMed - indexed for MEDLINE]

Display Show Sort by Send to

Related Links

Soluble receptors for tumor necrosis factor and interleukin-2 in serum and synovial fluid of patients with rheumatoid arthritis, reactive arthritis and osteoarthritis. [Rheumatol. 1995]

Soluble interleukin 6 (IL-6) receptor and IL-6 levels in serum and synovial fluid of patients with different arthropathies. [Rheumatol. 1997]

Interleukin-6, soluble interleukin-2 receptor and soluble interleukin-6 receptor in the sera of patients with different histological patterns of rheumatoid synovitis. [Rheumatol. 2003]

Soluble interleukin-2 receptor in sera and synovial fluids of rheumatoid patients: correlations with disease activity. [Rheumatol Int. 1994]

The effects of nonsteroidal antiinflammatory drug therapy in early rheumatoid arthritis on serum levels of soluble interleukin 2 receptor, CD4, and CD8. [Rheumatol. 1993]

[See all Related Articles...](#)

[Write to the Help Desk](#)

[NCBI](#) | [NLM](#) | [NIH](#)

[Department of Health & Human Services](#)

[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Jan 29 2007 05:15:30



A service of the National Library of Medicine
and the National Institutes of Health

My NCBI
[Sign In] [Register]

All Databases

PubMed

Nucleotide

Protein

Genome

Structure

OMIM

PMC

Journals

Books

Search PubMed for "Elevated soluble interleukin-2 receptor levels in the sera" Go Clear

Limits

Preview/Index

History

Clipboard

Details

Note: Performing your original search, "*Elevated soluble interleukin-2 receptor levels in the sera*", in PubMed will retrieve 102 citations.

Display AbstractPlus Show 20 Sort by Send to

All: 1 Review: 0

1: Arthritis Rheum. 1988 Jul;31(7):844-9.

Links

Elevated soluble interleukin-2 receptor levels in the sera and synovial fluids of patients with rheumatoid arthritis.

Keystone EC, Snow KM, Bombardier C, Chang CH, Nelson DL, Rubin LA.

Wellesley Hospital, Toronto, Ontario, Canada.

In a previous study, we used an enzyme-linked immunosorbent assay to measure soluble human interleukin-2 receptors (IL-2R), and found that when activated lymphocytes produce cell-associated IL-2R, they also release a soluble form of IL-2R into culture supernatants in vitro. Soluble IL-2R have also been detected circulating in vivo at low levels in the serum of healthy individuals, and at abnormal levels in a variety of diseases, particularly those where immune dysfunction is thought to play an important role. We therefore evaluated serum IL-2R levels in 77 patients with rheumatoid arthritis (RA), and compared them with levels in 46 age-matched healthy controls. Nineteen additional RA patients with concurrently obtained sera and synovial fluid (SF) samples were compared with 14 patients with osteoarthritis of the knee or hip. The serum IL-2R levels were significantly elevated in RA patients, compared with the control groups (P less than 0.0001). Serum IL-2R levels in the RA patients did not correlate with disease activity as determined by a variety of clinical and laboratory parameters. RA SF IL-2R levels were significantly higher than corresponding RA serum IL-2R levels (P = 0.0001). No such difference was noted in the osteoarthritis group, where serum and SF IL-2R levels were comparable with serum levels in healthy controls. These findings support the hypothesis that in vivo lymphocyte activation plays an important role in RA; moreover, soluble IL-2R measurement in serum and SF may be a very useful way to identify patients at risk for, or manifesting, a chronic immune-mediated inflammatory arthropathy.

Related Links

Soluble receptors for tumor necrosis factor and interleukin-2 in serum and synovial fluid of patients with rheumatoid arthritis, reactive arthritis and osteoarthritis. [Arthritis Rheum. 1995]

Soluble interleukin-2 receptor: elevated levels in serum and synovial fluid of patients with rheumatoid arthritis. [Clin Lab Anal. 1990]





Soluble interleukin-2 receptor in sera and synovial fluids of rheumatoid patients: correlations with disease activity. [Rheumatol Int. 1994]

Functional studies of soluble low-affinity interleukin-2 receptors in rheumatoid synovial fluid. [Arthritis Rheum. 1990]

Clinical and laboratory parameters which affect soluble interleukin-2 receptor levels in the serum and synovial fluids of patients with rheumatoid arthritis. [Dis Rheum Dis. 1993]

See all Related Articles...

PMID: 3134896 [PubMed - indexed for MEDLINE]

Display [AbstractPlus](#)  Show [20](#)  Sort by  Send to [Write to the Help Desk](#)[NCBI](#) | [NLM](#) | [NIH](#)[Department of Health & Human Services](#)[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Jan 29 2007 05:15:30



Registration open

Author Keywo
Vol Page

[HOME](#) [HELP](#) [FEEDBACK](#) [SUBSCRIPTIONS](#) [ARCHIVE](#) [SEARCH](#) [TABLE OF CONTENTS](#)

[Advanced]

Annals of the Rheumatic Diseases, 1993, Vol 52, 58-60

PAPERS

Serum concentrations of soluble interleukin 2 receptor in patients with rheumatoid arthritis: effect of second line drugs

A Crilly, R Madhok, J Watson and HA Capell

Department of Rheumatology, Gartnavel General Hospital, Glasgow, United Kingdom.

Serum soluble interleukin 2 receptor (sIL-2R) concentrations reflect lymphocyte activation in vivo. An investigation was carried out to determine if sIL-2R concentrations correlate with existing disease activity parameters in patients with rheumatoid arthritis (RA) and whether these concentrations are modulated by treatment with second line drugs. Seventy nine patients with rheumatoid arthritis with active disease were prospectively treated with sodium aurothiomalate, auranofin, or sulphasalazine. Sequential concentrations of sIL-2R were measured by enzyme linked immunosorbent assay (ELISA). No correlations were observed between sIL-2R concentrations and clinical parameters and there were only moderate associations with concentrations of C reactive protein and the erythrocyte sedimentation rate. Concentrations of sIL-2R did not significantly change with treatment. It is concluded that sIL-2R probably measures an aspect of rheumatoid synovitis distinct from acute phase reactants and is not influenced by treatment with second line drugs.

© 1993 by the Annals of the Rheumatic Diseases

This article has been cited by other articles: ([Search Google Scholar for Other Citing Articles](#))

This Article

- ▶ [Submit a response](#)
- ▶ [Alert me when this article is cited](#)
- ▶ [Alert me when eLetters are posted](#)
- ▶ [Alert me if a correction is posted](#)

Services

- ▶ [Email this link to a friend](#)
- ▶ [Similar articles in this journal](#)
- ▶ [Similar articles in PubMed](#)
- ▶ [Add article to my folders](#)
- ▶ [Download to citation manager](#)
- ▶ [Cited by other online articles](#)
- ▶ [Request Permissions](#)

Google Scholar

- ▶ [Articles by Crilly, A.](#)
- ▶ [Articles by Capell, H. A.](#)
- ▶ [Articles citing this Article](#)

PubMed

- ▶ [PubMed Citation](#)
- ▶ [Articles by Crilly, A.](#)
- ▶ [Articles by Capell, H. A.](#)

ANNALS OF THE RHEUMATIC DISEASES ▶ HOME

J. C Morris and T. A Waldmann

Advances in interleukin 2 receptor targeted treatment



Ann Rheum Dis, November 1, 2000; 59(90001): 1109 - 114.
[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

[HOME](#) [HELP](#) [FEEDBACK](#) [SUBSCRIPTIONS](#) [ARCHIVE](#) [SEARCH](#) [TABLE OF CONTENTS](#)



A service of the National Library of Medicine
and the National Institutes of Health

My NCBI
[Sign In] [Regis]

All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Book

Search PubMed for [] Go Clear

Limits Preview/Index History Clipboard Details

Display Abstract Show 20 Sort by Send to

About Entrez

Text Version

Entrez PubMed

Overview

Help | FAQ

Tutorials

New/Noteworthy

E-Utilities

PubMed Services

Journals Database

MeSH Database

Single Citation Matcher

Batch Citation Matcher

Clinical Queries

Special Queries

LinkOut

My NCBI

Related Resources

Order Documents

NLM Mobile

NLM Catalog

NLM Gateway

TOXNET

Consumer Health

Clinical Alerts

ClinicalTrials.gov

PubMed Central

1: Clin Immunol Immunopathol. 1994 Dec;73(3):296-304. Related Articles, Links



Comment in:

- Clin Immunol Immunopathol. 1995 Jul;76(1 Pt 1):102-4.

Serial measurement of serum interleukin-2 receptor levels in patients with rheumatoid arthritis: limited evidence for a role of T cell activation in clinical exacerbations.

Ward MM, Pyun E, Pisetsky DS.


Medical Service, Palo Alto Veterans Affairs Medical Center, California 94304.

To investigate the association of T cell activation with clinical exacerbations of RA, we measured serum levels of soluble interleukin-2 receptors (sIL2R), a marker of T cell activation, in serial samples obtained from 23 patients with RA. sIL2R measurements were performed on sera obtained from each patient every 2 weeks for up to 60 weeks, and levels were correlated with swollen joint counts, tender joint counts, physician global assessments, patient global assessments, pain scores, Health Assessment Questionnaire Disability Index scores, and Westergren erythrocyte sedimentation rates measured simultaneously. There were no significant correlations between changes in sIL2R levels and changes in any of the other measures, nor were lead-lag relationships detected, for the group as a whole. Examination of the time courses of individual patients revealed significant positive correlations between changes in sIL2R levels and changes in swollen joint counts in five patients; significant correlations with other measures were present in three or fewer patients. sIL2R levels also varied little over the 2-week time interval of greatest clinical change in each patient. These results suggest either that clinical exacerbations of RA are not associated with changes in T cell activation or that sIL2R levels do not accurately reflect such changes.

Publication Types:

- Research Support, U.S. Gov't, Non-P.H.S.
- Research Support, U.S. Gov't, P.H.S.

PMID: 7661913 [PubMed - indexed for MEDLINE]

Display **Abstract**  Show **20**  Sort by  Send to 

[Write to the Help Desk](#)
[NCBI](#) | [NLM](#) | [NIH](#)
Department of Health & Human Services
[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Jan 29 2007 05:15:30



A service of the National Library of Medicine
and the National Institutes of Health

My NCBI
[Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Book

Search PubMed for "Restricted cytokine expression in rheumatoid arthritis" Go Clear

Limits Preview/Index History Clipboard Details

Note: Performing your original search, "*Restricted cytokine expression in rheumatoid arthritis*", in PubMed will retrieve 48 citations.

Display AbstractPlus Show 20 Sort by Send to

All: 1 Review: 0

1: Arthritis Rheum. 1993 Jul;36(7):901-10.

Links

Restricted cytokine expression in rheumatoid arthritis.

Chen E, Keystone EC, Fish EN.

Department of Microbiology, University of Toronto, Ontario, Canada.

OBJECTIVE. To determine the cytokine profile of the phenotypically activated T cell in rheumatoid arthritis (RA) synovium. **METHODS.** Interleukin-2 (IL-2), IL-2 receptor (IL-2R), IL-6, IL-4, and interferon-gamma (IFN gamma) gene expression was examined in T cells from freshly isolated synovial fluids (SF) and synovial tissues (ST) from patients with RA. Estimates of baseline expression were determined using unstimulated peripheral blood (PB) T cells from healthy individuals. The corresponding positive controls were phytohemagglutinin-activated tonsil T cells. **RESULTS.** In studies of paired PB and SF T cell samples from 17 RA patients, IL-2 messenger RNA (mRNA) levels in only 1 PB and 3 SF samples were more than 2 standard deviations above the mean of levels in unstimulated PB from healthy donors. Similarly, only 5 PB and 7 SF samples exhibited elevated IL-2R mRNA levels. IFN gamma gene expression was not detected in any of the paired RA PB or SF samples. Fractionated T cells from 12 RA ST were screened with similar results: Only 1 of 12 samples exhibited IL-2 mRNA levels more than 2 standard deviations above levels in baseline controls. IL-2R mRNA levels were low or not detected, and IFN gamma mRNA was absent. Subsequent studies showed that IL-4 and IL-6 gene expression levels were also low in RA tissues compared with tonsil T cell-positive controls. **CONCLUSION:** These data provide evidence for restricted cytokine expression in the T cell population in RA tissues.

PMID: 8318038 [PubMed - indexed for MEDLINE]

Related Links

Analysis of Th1 and Th2 cytokines expressing CD4+ and CD8+ T cells in rheumatoid arthritis by flow cytometry. [J Rheumatol. 2000]

Decreased peripheral blood T cell cytokine gene expression in rheumatoid arthritis. [J Rheumatol. 1999]

Expression of interleukin 12 receptor (IL-12R) and IL-18R on CD4+ T cells from patients with rheumatoid arthritis. [J Rheumatol. 2004]

CCR3, CCR5, interleukin 4, and interferon-gamma expression on synovial and peripheral T cells and monocytes in patients with rheumatoid arthritis. [J Rheumatol. 2003]

Chemokine expression in rheumatoid arthritis (RA): evidence of RANTES and macrophage inflammatory protein (MIP)-1 beta production by synovial T cells. [J Rheumatol. 1995]

See all Related Articles...

Display AbstractPlus Show 20 Sort by Send to

[Write to the Help Desk](#)



A service of the National Library of Medicine
and the National Institutes of Health

www.pubmed.gov

My NCBI

[Sign In] [Register]

All Databases

PubMed

Nucleotide

Protein

Genome

Structure

OMIM

PMC

Journals

Books

Search PubMed



for

Go

Clear

Limits

Preview/Index

History

Clipboard

Details

Display AbstractPlus



Show

20



Sort by



Send to



All: 1

Review: 0



☐ 1: Semin Arthritis Rheum. 1992 Feb;21(4):239-45.

ELSEVIER
Full Text Article

Links

Immunohistologic study of T-cell receptor delta-chain expression in rheumatoid synovial membranes.

el-Gabalawy HS, Keillor J.

Section of Rheumatology, University of Manitoba, Winnipeg, Canada.

Lymphocytes expressing gamma delta T-cell receptors (TCRs) have been shown to be reactive to mycobacterial antigens as well as the so-called stress proteins. The detection of increased numbers of gamma delta cells in the synovial fluid and peripheral blood of some patients with rheumatoid arthritis has suggested a potential role for these lymphocytes in the pathogenesis of this disorder. Twenty-three rheumatoid synovial membranes were studied using immunohistology and monoclonal antibodies in an attempt to define the patterns of distribution of gamma delta T cells in rheumatoid synovitis. Consecutive sections were stained for T1(CD5), T4(CD4), T8 (CD8), TAC(CD25), the delta-chain markers delta TCR1 and delta TCS1, and the beta-chain marker beta F1. Our results show some regional differences in the distribution of CD4 and CD8 cells, the former being prominent in the lymphocytic aggregates and the latter most prominent in diffuse infiltrates immediately adjacent to the synovial lining layer. All tissues showed extensive staining for beta F1; an estimated average of more than 90% of T cells expressed alpha beta TCR. The majority of samples showed limited staining for both delta-chain antibodies, with 20 of the 23 tissues appearing to have less than 1% of T lymphocytes expressing these markers. Three tissues stained extensively for both delta TCR1 and delta TCS1 in particular areas of the section. In these areas, small perivascular lymphocytic aggregates appeared to be composed mainly of gamma delta cells. TAC staining was virtually absent in all areas and tissues. It was concluded that the majority of T lymphocytes infiltrating rheumatoid synovial membranes express alpha beta TCR. (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 1533291 [PubMed - indexed for MEDLINE]

Related Links

TCR gamma/delta+ cell subsets in the synovial membranes of patients with rheumatoid arthritis and juvenile rheumatoid arthritis. [Semin Arthritis Rheum. 1992]

Distribution of T-cell receptor-bearing lymphocytes in the synovial membrane from patients with rheumatoid arthritis. [J Autoimmun. 1990]

Immunohistological characteristics of T cell infiltrates in different forms of childhood onset chronic arthritis. [J Rheumatol. 1996]

T cells expressing gamma delta chain receptors in rheumatoid arthritis. [J Autoimmun. 1988]

T gamma delta cells in juvenile rheumatoid arthritis and rheumatoid arthritis. In the juvenile rheumatoid arthritis synovium the T gamma delta cells express activation antigens and are predominantly V delta 1+, and a significant proportion of these patients have elevated percentages of T gamma delta cells. [Scand J Immunol. 1990]

See all Related Articles...

Display AbstractPlus



Show

20



Sort by



Send to



[Write to the Help Desk](#)

[NCBI](#) | [NLM](#) | [NIH](#)
Department of Health & Human Services
[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Jan 29 2007 05:15:30



A service of the National Library of Medicine
and the National Institutes of Health

www.pubmed.gov

My NCBI

[Sign In] [Register]

All Databases

PubMed

Nucleotide

Protein

Genome

Structure

OMIM

PMC

Journals

Book

Search PubMed



for

Go

Clear

Limits

Preview/Index

History

Clipboard

Details

Display

AbstractPlus

Show

20

Sort by

Send to

All: 1

Review: 0



About Entrez

Text Version

Entrez PubMed

Overview

Help | FAQ

Tutorials

New/Noteworthy

E-Utilities

PubMed Services

Journals Database

MeSH Database

Single Citation Matcher

Batch Citation Matcher

Clinical Queries

Special Queries

LinkOut

My NCBI

Related Resources

Order Documents

NLM Mobile

NLM Catalog

NLM Gateway

TOXNET

Consumer Health

Clinical Alerts

ClinicalTrials.gov

PubMed Central

1: Exp Med. 1988 Nov 1;168(5):1573-86.



Full Text
Exp Med

Cytokines in chronic inflammatory arthritis. I. Failure to detect T cell lymphokines (interleukin 2 and interleukin 3) and presence of macrophage colony-stimulating factor (CSF-1) and a novel mast cell growth factor in rheumatoid synovitis.

Firestein GS, Xu WD, Townsend K, Broide D, Alvaro-Gracia J, Glasebrook A, Zvaifler NJ.

Department of Medicine, University of California, San Diego 92103.

Because previous studies showed low levels of IFN-gamma in rheumatoid arthritis (RA) synovial fluid (SF) and synovial tissue (ST) explant supernatants, we assayed RA SF and ST for IL-2 and IL-3-like activity. Using an IL-2 dependent murine CTLL line, 6 of 14 RA SF caused increased thymidine uptake (greater than three times control). The activity was distinct from IL-2 because it was not blocked by antibody to IL-2-R. In addition, IL-2 was not detected (less than 50 pg/ml) in 16 joint samples using an ELISA. Multi-colony-stimulating factor (CSF) activity was measured using two assays that can detect murine IL-3 (mast cell proliferation, and bone marrow CSF). In the mast cell assay, [3H]TdR uptake was 493 +/- 67 cpm for medium, 2,910 +/- 329 cpm in the presence of RA SF (p less than 0.001), 1,246 +/- 156 cpm in the presence of SF from patients with seronegative spondyloarthropathies (p less than 0.001), and 736 +/- 100 cpm in the presence of osteoarthritis SF (p greater than 0.1). In the CSF assay, four of five RA SF and five of five RA ST induced colony formation from bone marrow nonadherent cells. Macrophage colonies were most common, although mixed colonies and granulocytes were occasionally observed. The multi-CSF activity in RA is not due to IL-3 since human rIL-3 was not active in either murine assay, and IL-3 mRNA was not detected in RA synovium. Sephadex column chromatography of RA SF revealed that the mast cell growth factor (approximately 6 x 10(3) mol wt) and the CSF (approximately 40 and 100 x 10(3) mol wt) are distinct. The colony-stimulating aspect of the "IL-3-

Related Links

Cytokines in chronic inflammatory arthritis. Granulocyte-macrophage colony-stimulating factor in rheumatoid synovitis.

Anti-proliferative effect of gamma in immune response. IV. Murine CTL clone IL-3 and GM-CSF, the which is masked by the inhibitory action of secreted IFN-gamma. [J Immunol]

Interleukin-10 function in antiinflammatory cytokine production in rheumatoid arthritis.

Cytokines in chronic inflammatory arthritis. Granulocyte/macrophage colony-stimulating factor mediated induction of MHC antigen on human monocytes: a possible role in rheumatoid arthritis.

Inhibition of the growth of dependent mast cells by murine bone marrow recombined granulocyte-macrophage colony-stimulating factor. [J Immunol]

See all Related Articles

like" activity in RA SF is likely due to CSF-1 because it is the appropriate mol wt and because the activity was neutralized by specific anti-CSF-1 antibody. Finally, an RIA detected 1.6-25 ng/ml of CSF-1 in RA SF and ST and CSF-1 mRNA was detected in four of five RA synovial tissue samples tested.

PMID: 3263464 [PubMed - indexed for MEDLINE]

Display [AbstractPlus](#)  Show [20](#)  Sort by  Send to 

[Write to the Help Desk](#)

[NCBI](#) | [NLM](#) | [NIH](#)

[Department of Health & Human Services](#)

[Privacy Statement](#) | [Freedom of Information Act](#) | [Disclaimer](#)

Jan 29 2007 05:15:30